PERSEVERATIVE NEGATIVE THINKING PREDICTS DEPRESSION IN PEOPLE WITH ACUTE CORONARY SYNDROME

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Competing interests

The authors have no competing interests to declare.

Abstract

Objective: Depression is common in people who have experienced recent Acute Coronary Syndrome (ACS), and predicts worse medical outcomes. Mechanisms underpinning the development of depression and its association with poor medical outcomes are unclear however. The aim of this study was to investigate the role of perseverative negative thinking (e.g. worry and rumination) in predicting depression in people with recent ACS.

Methods: Adults attending specialist inpatient and outpatient cardiology services who had recently experienced ACS were invited to participate in this observational prospective cohort study. Questionnaire assessments were completed within 6 months of index ACS (baseline), then 2 months and 6 months later.

Results: 169 participants (131 male (78%), median age 68 (±16) years) completed baseline questionnaires, and 111 completed follow-ups. After controlling for the effects of key covariates, baseline rumination was a significant predictor of depression at 6 months, accounting for 2% of the variance in depression. This association was partially mediated by poor problem-solving ability and lack of social support. Neither worry nor rumination at baseline were significant predictors of quality of life at 6 months.

Conclusions: Rumination is a significant independent predictor of depression, and this association may be partially explained by deficits in problem-solving ability and reduced social support. Both rumination and problem solving may provide useful targets for the development of evidence-based interventions to reduce depression among people with coronary heart disease.

Keywords

Depression, worry, rumination, problem solving, coronary heart disease, prospective study

Background

Forty per cent of people who experience Acute Coronary Syndrome (ACS) will suffer from significant depression in the weeks or months following their cardiac event (Rudisch & Nemeroff, 2003; Thombs et al., 2006). Depression following ACS is important as it is associated with worse physical health outcomes, including worse health-related quality of life (Dickens, Cherrington, & McGowan, 2012; Dickens et al., 2006), greater use of unscheduled care (Dickens, Katon, et al., 2012), greater healthcare costs (Frasure-Smith et al., 2000; Rutledge et al., 2009) and doubling of the risk of subsequent morbidity and mortality (Barth, Schumacher, & Herrmann-Lingen, 2004; Nicholson, Kuper, & Hemingway, 2006; Van Melle et al., 2004). A number of risk factors for post ACS depression have been proposed (Dickens et al., 2004; Doyle, McGee, Delaney, Motterlini, & Conroy, 2011), though findings have been mixed and mechanisms linking depression to adverse health outcomes have not been established (Dickens, 2015).

Perseverative negative thinking describes worrying (experience of a chain of thoughts / images, which are future-focussed, negatively affect laden and relatively uncontrollable) and rumination (repetitive thought around a personal theme in the absence of any external cues to provoke such thoughts) e.g. Ehring & Watkins, 2008; Watkins, 2008. Perseverative negative thinking is a common, everyday phenomenon, and several strands of evidence suggest it is associated with negative effects on mood in otherwise healthy samples: i) it is elevated in people at greater risk for depression e.g. females and individuals with a history of depression(Butler & Nolen-Hoeksema, 1994; Johnson & Whisman, 2013; Riso et al., 2003), ii) empirical studies show cross-sectional and prospective associations between perseverative negative thinking and adverse mental health outcomes (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Mor & Winquist, 2002; Teismann, Steinfeld, Willutzki, & Michalak, 2011; Thomsen, 2006; E. R. Watkins, 2008), and iii) experimental studies show that inducing perseverative negative thinking increases depressed and anxious mood(Behar, Zuellig, & Borkovec, 2005; Blagden & Craske, 1996; Ciesla & Roberts, 2007; Conway,

Csank, Holm, & Blake, 2000; McLaughlin, Borkovec, & Sibrava, 2007). Recent findings in non-cardiac populations indicate that perseverative negative thinking predicts the onset, maintenance and relapse of depression (Borkovec, Robinson, Pruzinsky, & DePree, 1983; Calmes & Roberts, 2007; Ciesla & Roberts, 2007; Conway et al., 2000; Just & Alloy, 1997; McLaughlin et al., 2007; Morrow & Nolen-Hoeksema, 1990; Nolen-Hoeksema, 2000; Nolen-Hoeksema & Morrow, 1991; Nolen-Hoeksema & Morrow, 1993; Nolen-Hoeksema, Morrow, & Fredrickson, 1993; Segerstrom, Tsao, Alden, & Craske, 2000; Spasojević & Alloy, 2001) with evidence that this may in part be due to interference with effective problem solving, engagement in instrumental rewarding behaviours or access to social support, which have been proposed as mediators of the negative effects of rumination (Lyubomirsky & Tkach, 2004; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008; E. R. Watkins, 2008). That is, by exacerbating negative, pessimistic thinking rumination leads to low problem-solving confidence, lack of motivation to initiate active responses, and to behaviour that is counterproductive to maintaining supportive relationships. For example, previous studies have shown both that i) rumination interferes with multiple aspects of problem solving. For example, ruminators, compared to non-ruminators, lack confidence in the quality of their problem solutions and are less likely to implement problem solutions (McMurrich & Johnson, 2008; Ward, Lyubomirsky, Sousa, & Nolen-Hoeksema, 2003), and experimental studies that induce individuals to ruminate lead to impairments in problem solving (Lyubomirsky, Tucker, Caldwell, & Berg, 1999; E. Watkins & Baracaia, 2002), and ii) poor problem solving is prospectively associated with depressive and anxious symptoms and it mediates the association of stressful life events with depression and anxiety (Anderson, Goddard, & Powell, 2011; Kant, D'Zurilla, & Maydeu-Olivares, 1997; Nezu, 1985; Nezu & Ronan, 1988). Similarly, ruminators appear to engage in behaviours that erode social support such as placing high emotional and practical demands on members of their social network, excessive reassurance-seeking, and creating conflict and disturbances in their interpersonal relationships due to dissatisfaction with perceived support (Flynn, Kecmanovic, & Alloy,

2010; Keefe et al., 2003; Weinstock & Whisman, 2007). In turn, the inability to form and maintain close relationships, low perceived availability of social support, and the number of close network members have all been associated with depression, anxiety and worse quality of life in people with CHD (Bosworth et al., 2000; Brummett et al., 1998; Dickens et al., 2004; Holahan, Moos, Holahan, & Brennan, 1997; Oxman & Hull, 1997; Simning, Seplaki, & Conwell, 2016; Vaglio et al., 2004).

Furthermore, perseverative negative thinking may predict adverse physical outcomes such as worse cardiovascular health, impaired wound healing and immune dysfunction (Broadbent, Petrie, Alley, & Booth, 2003; Kubzansky et al., 1997; Segerstrom, Solomon, Kemeny, & Fahey, 1998), by prolonging the physiological activation associated with stress (Brosschot, Gerin, & Thayer, 2006; Pieper, Brosschot, van der Leeden, & Thayer, 2010; Siegle, Steinhauer, Carter, Ramel, & Thase, 2003). Thus, the way people think about their illness may impact on their physical as well as psychological wellbeing. For example a systematic review by Foxwell, Morley & Frizelle (2013) showed that negative beliefs about illness predicted worse quality of life as well as depression. However few studies have examined the impact of perseverative negative thinking on depression and physical health outcomes in the same population. A recent systematic review identified only one study of perseverative negative thinking in patients following ACS that investigated effects on both depression and physical health outcomes (Trick, Watkins, Windeatt, & Dickens, 2016). The study found that rumination predicted subsequent depression, but did not predict subsequent health-related quality of life (Baker, 2014), although this study did not use a recommended method for scoring the quality of life measure, which may have obscured an association.

Better understanding the causes of depression following ACS and the mechanisms linking it to worse physical health outcomes could lead to the development of novel interventions to treat or even prevent depression, and possibly reduce its adverse impact on physical health

outcomes. For example, perseverative negative thinking could provide a treatment target to improve both depression and physical health outcomes after ACS. To this effect, we conducted a prospective cohort study among people who had experienced recent ACS to determine the effects of perseverative negative thinking on both psychological and physical health outcomes. We used health-related quality of life as a measure of physical health outcomes. To extend previous research, we included measures of both rumination and worry, and investigated plausible mechanisms (i.e. impaired problem-solving, reduced instrumental behaviours and low social support) mediating the effects of perseverative negative thinking on depression.

Our study tested the primary hypothesis that, among individuals who had experienced ACS in the previous 6 months rumination and worry at baseline would predict depression, generic and cardiac specific health-related quality life 6 months later. Previous studies have shown that rumination is associated with subsequent depression in patients with coronary heart disease over short durations (Baker, 2014; Denton, Rieckmann, Davidson, & Chaplin, 2012), although it is unclear if these findings extend to other forms of perseverative negative thinking such as worry, or if perseverative negative thinking predicts other outcomes such as quality of life in this group. We also tested the secondary, exploratory, hypothesis that the effects of baseline rumination and worry on depression at 6 months would be mediated by: a) reduced social support, b) impaired problem solving, and c) reduced instrumental behaviours. Research in non-cardiac populations suggests these factors may be important in explaining the association of rumination with depression (Lyubomirsky & Tkach, 2004; Nolen-Hoeksema et al., 2008; E. R. Watkins, 2008), however to our knowledge this is the first study to explore social support, problem solving and instrumental behaviours as mediators of this relationship in people with ACS.

Methods

Participants

Adults attending specialist inpatient and outpatient cardiology services at a teaching hospital in south west England between September 2014 and May 2015 were eligible for recruitment if they met the following inclusion criteria: i) they were aged 18 years or over, and ii) they had experienced ACS, including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina, in the previous 6 months.. Patients were excluded from the study if: i) they were considered too frail or physically unwell, or ii) it was deemed inappropriate by a member of the clinical team to approach the patient for research because they were suffering from severe mental illness (including psychosis or severe depression with significant active suicide risk).

A sample size calculation indicated that 113 participants assessed at baseline, 2 months and 6 months would provide 90% power to detect a bivariate association of 0.30 at the p=0.05 significance level. A similar previous study in ACS patients found a correlation of r=0.49 between baseline brooding and depression at 3 month follow-up (Denton et al., 2012) and so r=0.30 represents a conservative estimate. We expected that this number of subjects would provide sufficient power to conduct multivariable regression analyses using up to 8 independent variables (Green, 1991).

Design and procedure

Our study used an observational prospective cohort design. Baseline information was collected and initial questionnaire assessments administered within 6 months of index ACS (baseline).Questionnaire assessments were repeated 2 months and 6 months later.

Full ethical permission from the South West – Frenchay Research Ethics Committee was obtained prior to commencement of this study. All participants provided written informed consent.

Baseline assessments

We used a custom-designed questionnaire to record the following details: age, sex, employment status, occupation, years of education, relationship status, living situation, frequency of exercise, cigarette, alcohol and recreational drug use. Index of Multiple Deprivation (IMD) decile was derived from the participants current postcode and used as a proxy for socioeconomic status ("The English indices of deprivation statistical release," 2015).

The following information was extracted from paper and electronic medical records: cardiac diagnosis at index admission (unstable angina/STEMI/NSTEMI), days since index event, severity of cardiac disease (number of diseased coronary vessels, left ventricular function, troponin at hospital admission), blood markers of inflammation at hospital admission (C-reactive protein, white cell count), pre-existing physical health conditions, current medication and history of depression (a binary variable i.e. 'yes' / 'no', based upon evidence of a positive history recorded in paper or electronic notes). Number and severity of comorbidities was assessed using the Charlson Co-morbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987; Peterson, Paget, Lachs, Reid, & Charlson, 2012). A self-rated version of the New York Heart Association (NYHA) functional status classification system was used to assess limitations of physical activity due to chest discomfort, palpitations, shortness of breath and fatigue (Dolgin, 1994).

Questionnaire measures at baseline, 2 months and 6 months

Worry was assessed using the 16-item Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990) . The PSWQ has been shown to correlate with depression in patients with long term conditions including CHD (Dickens, Coventry, et al., 2012). It has good test-retest reliability ($r>0.90$) and high internal consistency (Cronbach $\alpha>0.88$) in undergraduates, community volunteers and older adults with anxiety disorders (Beck, Stanley, & Zebb, 1995; Brown, Antony, & Barlow, 1992; Meyer et al., 1990). In this

sample Cronbach α=.91. The 5-item brooding subscale of the self-report Ruminative Responses Scale (RRS; Nolen-Hoeksema & Morrow, 1991) was used to measure rumination. The brooding subscale contains items that capture the tendency towards "moody pondering" involving repeated passive, abstract, and negative comparisons and evaluations, when feeling sad or down (Treynor, Gonzalez, & Nolen-Hoeksema, 2003), e.g., "Think "Why can't I handle things better?", "Think "Why do I always react this way?". Use of this subscale avoids inclusion of 'depression contaminated' items that can inflate apparent associations between rumination and depression. The RRS brooding subscale correlates with measures of negative mood and onset, maintenance and severity of depression (e.g. (Just & Alloy, 1997; Nolen-Hoeksema, 2000; Segerstrom et al., 2000)) in samples including ACS patients (Denton et al., 2012). It has previously been shown to have good internal consistency (Cronbach α=.77) and test-retest reliability (r=0.62)(Treynor et al., 2003). In this sample Cronbach α =.85. For both worry and rumination assessments high scores reflected higher levels of trait perseverative negative thinking.

Depression was assessed using the 8-item Patient Health Questionnaire (PHQ-8), which rates how often in the past two weeks people have experienced each of eight depressive symptoms, such that higher scores indicate greater severity of depression (Hayek et al., 2017; Kroenke et al., 2009; Razykov, Ziegelstein, Whooley, & Thombs, 2012). The PHQ-8 is recommended in medically ill patients, including CHD patients, since passive thoughts of death (unrelated to suicidal intent) may be more common among this group than in the general population meaning that the ninth item may not represent an accurate suicide screen (Razykov et al., 2012). Psychometric properties of the PHQ-8 are equivalent to the more commonly used 9 item version (PHQ-9), with sensitivity and specificity of 88% for detecting depressive disorders using a cut point of ≥10 (Kroenke, Spitzer, Williams, & Lowe, 2010; Kroenke et al., 2009). Internal consistency of the PHQ-8 is high, with Cronbach α=0.86 in a previous study (Ory et al., 2013), and α=0.89 in this sample. Generic health-related quality of life was assessed using the index value and visual analogue scale (VAS) of

the EuroQol-5D (EQ5D; EuroQol Group, 1990; Herdman et al., 2011). The EQ5D has been used extensively in cardiovascular research and its validity and reliability in this population is supported (e.g.(Dyer, Goldsmith, Sharples, & Buxton, 2010; Schweikert, Hahmann, & Leidl, 2006)). Cardiac disease-specific health-related quality of life was assessed with the Seattle Angina Questionnaire (SAQ; physical limitations, frequency of angina, stability of angina, treatment satisfaction, and disease perception subscales). Internal consistency of the SAQ subscales is good in people with coronary heart disease (Cronbach α=0.67 to 0.91)) (Kimble et al., 2002; Spertus et al., 1995).

Measures of possible mediators at baseline, 2 months and 6 months

We assessed variables that have been proposed to mediate the effects of perseverative negative thinking on depression (Nolen-Hoeksema et al., 2008), including: i) reduced social support, using the Enhancing Recovery in Coronary Heart Disease study Social Support Inventory (ESSI)(Mitchell et al., 2003), ii) impaired problem solving, using the Social Problem Solving Inventory-revised short version (SPSI-R:S) (D'Zurilla, Nezu, & Maydeu-Olivares, 2002; Nezu & Ronan, 1988) and iii) reduced instrumental behaviours, using the 20-item short version of the Pleasant Events Schedule for the elderly (PES-E) (MacPhillamy & Lewinsohn, 1982). The psychometric properties of each of these instruments have previously been demonstrated: 1) the ESSI has been shown to correlate with the social functioning subscale of the Short Form-36, and its internal reliability (Cronbach α=0.88) and test-retest reliability (r=0.94) are good (Vaglio et al., 2004); 2) internal consistency (Cronbach α≥0.80) and test-retest reliability (r=0.68 to r=0.91) of the SPSI-R:S are good, and normative data is available for healthy adults and clinically depressed populations (D'Zurilla et al., 2002; Hawkins, Sofronoff, & Sheffield, 2009); and 3) the PES-E correlates well with the original long version of the Pleasant Events Schedule, which correlates with daily diary reports of activity (r=0.68 to 0.81) and depression scores (MacPhillamy & Lewinsohn, 1982). Higher ESSI, SPSI-R:S and PES-E scores indicate greater availability of

social support, a more negative attitude to problem solving and greater engagement in instrumental behaviours, respectively.

Statistical analyses

Descriptive statistics are presented using median and interquartile range for continuous variables, and number and percentages for categorical variables. Comparison of variables across categories was made using the Mann-Whitney U test or Chi-Square test, as appropriate.

Predictors of depression and quality of life at 6 months

To investigate if baseline worry or rumination predicted depression or worse quality of life at 6 months, a series of staged multivariable linear regression analyses were conducted. In separate models, the outcome at 6 months (continuous variables in each case) was depression, general health-related quality of life and cardiac disease-specific quality of life. Predictors were entered in 3 successive blocks: i) age, sex, socioeconomic status, social support, history of depression, severity of cardiac disease, ii) baseline scores for the outcome variable, iii) baseline worry or baseline rumination, as appropriate. In order to account for the effects of demographic and other variables known to be associated with depression in people with coronary heart disease the variables in step 1 were entered as covariates (e.g. (Dickens et al., 2004; Egede, 2007; Holahan et al., 1997). Similarly baseline scores for the outcome variable of interest (e.g. baseline depression) were entered separately into step 2 of the model to isolate the extent to which baseline scores on the outcome variable would predict subsequent scores on the same variable at 6 months, and to test the added value of worry and rumination in predicting depression after accounting for baseline outcome scores.

Mediators of the association between perseverative negative thinking and depression

We explored the roles of social support, problem solving and instrumental behaviours as potential mediators of the prospective association of perseverative negative thinking at baseline with outcomes at 6 months using a causal steps approach, based on the methods of Baron & Kenny (1986). A series of 3 regression analyses were conducted for each set of predictor, mediator and outcome variables: 1) outcome at 6 months regressed on predictor at baseline, 2) proposed mediator at 2 months regressed on predictor at baseline, and 3) outcome at 6 months regressed on both predictor at baseline and mediator at 2 months, in the same model. Mediation was considered to have occurred if all of the following conditions were met (see Figure 1A for illustration):

i. The predictor significantly predicted the outcome (the total, unadjusted, effect of predictor on outcome, *path c'*).
ii. The predictor significantly predicted the proposed mediator (the direct effect of predictor on mediator, *path a*).
iii. The proposed mediator significantly predicted the outcome in a model that also includes the predictor (*path b*, the direct effect of mediator on outcome).
iv. The regression coefficient of the predictor in a model that also includes the mediator (*path c*, the direct effect of predictor on outcome) was smaller than the coefficient of the total effect (*path c'*).

If the causal steps approach indicated findings consistent with mediation, a bootstrapping method with 5000 samples and bias corrected confidence intervals was used to determine significance of the mediated effect (Preacher & Hayes, 2004).

To evaluate the impact of missing data on our findings, the final step of each of the staged multivariable linear regression models and mediation analyses based on complete cases (as described above) was replicated using imputed datasets, generated using multiple imputation by chained equations (MICE). The overall model fit and beta coefficients were compared with results using complete cases analyses. In all cases the contributions of worry

and rumination to the regression models were unchanged when imputed data were used, compared to the findings using complete case analysis. For brevity, only findings for the complete case analyses are presented in this report.

All analyses were conducted using Stata SE statistical software release 14 (StataCorp. 2015; College Station, TX).

Results

The flow of participants through each stage of recruitment and participation in the study is summarised in Appendix 1 (see Supplementary Materials). Demographic and disease characteristics for the 169 participants who completed baseline questionnaires are summarised in Table 1. Participants who consented did not differ significantly in age or sex compared to those who declined to be involved (p's > 0.05).

Twenty-four participants (14.4%) were depressed (PHQ≥10) at baseline. Participants with depression were younger (61.5 vs. 68 years; z=3.37, p=0.007), less likely to be in a relationship (23.3% vs 50.0%, $\chi^2(1)=7.44$, p=0.006), more likely to live alone (45.8% vs. 21.8%, $\chi^2(1)=6.26$, p=0.012), have a history of depression (29.2% vs. 6.3%, $\chi^2(1)=12.41$, p=0.000), be smokers (33.3% vs. 7.0%; $\chi^2(1)=14.68$, p=0.000), exercise infrequently (48.5% vs. 30.5%; $\chi^2(1)=5.13$, p=0.024) and have lower socioeconomic status (70.8% in most deprived deciles vs. 46.0%; $\chi^2(1)=5.04$, p=0.025). More of the subgroup of participants with depression had raised C-reactive protein (CRP>10mg/L) during hospital admission compared to those without depression (64.3% vs. 36.3%; $\chi^2(1)=3.83$, p=0.050).

Follow-up assessments

First follow-up assessments were conducted a median of 84 days (IQR=32) and second follow-up assessments 195.5 days (IQR=31.5) from baseline. Of 169 participants who completed baseline assessments, 58 participants did not complete the 6 month questionnaire pack (i.e. 34.3%). Of these 3 were too unwell, 4 withdrew, 2 died, and 49 did

not respond to repeated requests to return the questionnaire pack. Compared to completers, non-completers at 6 months were more likely to have raised white cell count (41.1% vs. 24.3%; $\chi^2(1)=4.92$, p=0.027) and raised CRP (55.6% vs. 30.9%; $\chi^2(1)=5.48$, p=0.019) at hospital admission. There was no significant difference in PHQ-8 scores at baseline between completers (median=2, IQR=4) and non-completers (median=3, IQR=7; z=1.26, p=0.209) at 6 months.

Prospective associations of baseline predictors with outcomes at 6 months

Predictors of depression

The model including baseline rumination in the third step predicted 64% of variance in 6 month depression ($F(8,97)=24.68$, $p\leq0.001$). Social support, depression and rumination at baseline were significant predictors of 6 month depression, with rumination contributing 2% to the overall variance of 6 month depression ($p\leq0.05$, Table 2). In a separate model with baseline worry entered in the third step, whilst the overall model accounted for 60% of the variance in 6 month depression ($F(8,98)=20.83$, $p\leq0.001$), with social support and depression at baseline significant predictors of 6 month depression, baseline worry did not contribute to the final model (change in $R^2=0\%$) (Table 2).

Predictors of health-related quality of life

Final regression models predicting EQ5D index value, EQ5D VAS and SAQ subscales were significant though neither baseline worry nor rumination contributed to the final models. Results are reported in full in Appendix 2 (EQ5D index value and VAS) and Appendix 3 (SAQ subscales) (see Supplementary Materials).

Time since ACS and time of follow-up assessments

Since there was some variability among the final sample in time from index event (i.e. onset of ACS) and in the time at which follow-up assessments were completed (i.e. time from baseline), we explored the effect of these potentially important variables by entering them as

additional covariates into our staged multivariable regression models in which depression at 6 months was the outcome variable. Time since ACS did not significantly predict depression at 6 month follow-up, and the addition of time since ACS did not substantially alter the overall model ($F(9,92)=20.21$, $p \leq 0.001$) or any other associations. Time since baseline was a significant predictor of depression at 6 month follow-up ($\beta=-0.14$, $p=0.018$), but its addition as a covariate did not substantially alter the overall model ($F(9,96)=23.67$, $p \leq 0.001$) or any other associations. Results are reported in Appendix 4 (see Supplementary Materials).

Impact of missing data

58 participants did not complete follow-up assessments at 6 months. We explored the impact of missing data by repeating the third and final step of each of the staged multivariable regression models using multiple imputation for chained equations. The findings were consistent with those of the models using non-imputed data. Findings for models predicting 6 month depression are presented in Appendix 5 (see Supplementary Material).

Possible mediators of the association between baseline rumination and depression at 6 months

Using our causal steps approach, simple, unadjusted regression models indicated that baseline rumination was associated with depression at 6 month follow-up via i) low perceived availability of social support, ii) greater negative problem orientation and iii) low engagement in pleasant activities at 2 month follow-up (Table 3). In each case rumination at baseline remained a significant predictor of depression at 6 month follow-up after controlling for the potential mediating variable at 2 months, consistent with partial mediation. In line with these findings, bootstrap tests of the indirect effects were significant, and indicated that 10.5%, 40.2% and 9.3% of the total effect of rumination on depression was mediated by low social support, negative problem orientation and reduced engagement in pleasant activities, respectively.

Multiple mediation

We used a multiple mediation model to investigate the combined effects of social support, negative problem orientation and engagement in pleasant activities at 2 months as mediators of the association between baseline rumination and 6 month depression. In this model, low perceived availability of social support and greater negative problem orientation at 2 month follow-up, but not engagement in pleasant events at 2 months, were independent predictors of 6 month depression. Rumination at baseline remained a significant predictor of depression at 6 month follow-up after controlling for the potential mediating variables at 2 months, consistent with partial mediation. A bootstrap test of the indirect effect was significant, and the proportion of the total effect mediated by the combination of low social support and impaired problem solving was 40.3%. The regression coefficient representing the direct association of problem solving with depression was larger than the coefficient representing the direct association of social support with depression suggesting that problem solving was the strongest mediator. The results are shown in Figure 1B.

Discussion

In this prospective observational cohort study of patients with an acute coronary syndrome (ACS), baseline rumination was a significant predictor of depression 6 months later, after controlling for baseline depression, consistent with our hypotheses. This association persisted after controlling for variables known to be associated with depression, and was mostly mediated by poor problem-solving ability, but also by reduced social support. Inconsistent with our hypotheses, neither worry nor rumination significantly predicted subsequent health-related quality of life.

Particular strengths of our study include our prospective design, which allows us to draw some tentative causal inferences from our findings, though these fall short of proving causation. Furthermore, the self-report measures of perseverative negative thinking used in this study were selected carefully to minimise artefactual associations between rumination

and depression. Finally, our regression models were very conservative in that they controlled both for i) important co-variates that are recognised to be associated with both depression and / or quality of life in people with ACS (Dickens et al., 2006; Dickens et al., 2004), which could confound the associations of perseverative negative thinking with depression and quality of life, and ii) baseline scores for each outcome of interest, since baseline scores would be highly correlated with scores at follow-up, in particular baseline depression, which is commonly found to be a strong predictor of subsequent depression.

The main limitation of our study was the relative high level of attrition. Only 66% of recruited participants completed assessments at 6 months, which is lower than similar recent studies using postal follow-up assessments (Baker, 2014; Garnefski, Kraaij, De Graaf, & Karels, 2010). Our high rates of participant attrition will have reduced our power to detect associations between predictors and outcomes of interest. As a consequence, we acknowledge that a broader range of predictors may have been identified in a larger study, though our methods will have identified the strongest predictors of interest. Also, our high attrition may have resulted in a participant selection bias that could limit generalisability of our findings. Those dropping out had high levels of markers of inflammation at admission, which could indicate more severe cardiac disease, though there were no other differences. Analyses repeated using imputed missing values provided the same results as for participants who remained in the study, so we do not believe that participant attrition undermined our findings.

There was some variability between participants in time from ACS, and also in the timing of follow-up assessments in this study. Neither time from ACS nor the interval between baseline assessments and 6 month follow-up significantly impacted upon our overall models, although our findings suggested that depression scores were greatest when the interval between baseline and 6 month follow-up assessments was smallest. It is unclear how the temporal relationship of depression and CHD evolves ((Freedland & Carney, 2013; Thombs et al., 2006)) or how the time course of rumination following CHD may unfold, and it is

possible that the optimal timings of effects may have been missed here, meaning our results could represent an underestimate of associations.

The causal steps approach we adopted relies on the correct specification of the underlying regression models and may give biased results if, for example, there are omitted variables that confound the relationship between predictors and mediators, or between mediators and outcomes. Strengths of the design which aid the internal validity include the timing of the measurements (with mediator measured after predictor, and outcome measure after mediator) and adjustment for baseline outcomes and other covariates which may reduce unmeasured confounding. A bootstrapping approach was used to address non-normality of the sampling distribution when testing the indirect effects. We used bias-corrected confidence intervals since power was a concern. However, due to our small sample size, we cannot conclude that other mediating variables are unimportant in explaining the association of rumination with subsequent depression, merely that poor problem solving and lack of social support were important predictors of depression among our participants. These findings should be confirmed in a larger sample which would provide greater statistical power to detect important mediating variables.

Consistent with previous studies (e.g. Denton, Rieckmann, Davidson & Chaplin, 2012), our findings indicate that brooding rumination (the tendency for individuals to passively and abstractly make negative comparisons when feeling sad or down) predicts subsequent depression in people with recent ACS (Trick et al., 2016). Among this cohort of post-ACS patients, the effects of rumination on depression were mediated mainly by impairment in problem solving capacity, particularly negative problem orientation which reflects a tendency to feel threatened, nervous, frustrated or upset when faced with a problem. This finding has face validity and it seems likely that ruminating about one's life situation extends to thinking pessimistically about one's problems and the ability to resolve them. To a lesser extent the effects of rumination on depression were mediated via interference with social support, although since the assessment of social support was self-reported, it is unclear whether this

is the result of an actual reduction in availability of social support or simply the perception that support is reduced.

We found a small but significant association of rumination with depression in this study (rumination at baseline accounted for 2% of variance in depression at follow-up). Baseline depression was a particularly strong predictor of depression at follow-up, possibly because the sample included in this study appeared to be particularly 'well'. Since a large amount of variance was accounted for by baseline depression, small but significant effects of other variables could have been masked and the effect sizes of brooding (and worry) could have been underestimated. Future research should include participants with depression at baseline, as this may allow other predictors with small but important effects to emerge. Similarly, history of depression is important because it is associated with post-MI depression, at least in a subgroup of patients, and depression that precedes an MI could have different risk factors compared to depression that develops post-MI e.g.(Dickens, 2015). We ascertained history of depression by retrospectively inspecting medical records. Although this could be considered a more reliable method of identifying patients with significant depressive disorder than self-reports, it may lack sensitivity to identify less severe depressive episodes or transient mood disturbances, and did not allow us distinguish between symptoms of depression that emerged before vs. after the onset of ACS. It is unclear therefore how the timing of previous episodes of depression may impact on depression following ACS. Future studies should collect history of depression from self-reports or from diagnostic clinical interviews, which would provide more detailed information regarding previous episodes and duration of current episode if applicable.

Contrary to expectations, we did not find worry predicted subsequent depression, which contradicts findings from a cross-sectional study among a mixed population of individuals with diabetes, chronic pulmonary disease and rheumatoid arthritis (Dickens, Coventry, et al., 2012). Differences from this earlier study may be attributable to the inclusion of participants with different physical conditions with different clinical outlooks, or could be due to the

rigorous prospective study design of our more recent study. Similarly, we found no association of worry or rumination with cardiac-specific or generic health-related quality of life. This is surprising, considering that previous research has found associations of worry and rumination with a range of adverse physical health outcomes including impaired wound healing (Broadbent et al., 2003), immune dysfunction (Segerstrom et al., 1998), worse functional outcomes in rheumatoid arthritis and psoriasis (Evers, Kraaimaat, Geenen, & Bijlsma, 1998; Fortune et al., 2003) and worse cardiac outcomes (Kubzansky et al., 1997). It may be that the use of a multidimensional health-related quality of life as an outcome obscured the associations seen with more specific, and sometimes physiological, measures used in previous research.

Our findings suggest that screening for individuals experiencing negative ruminative thoughts following ACS could help identify those at greater risk of subsequent depression. Future research should include further examination of perseverative negative thoughts on health outcomes, ideally in larger populations, with longer follow-up and including more objective measures of health outcomes along with health-related quality of life. Furthermore, interventions to reduce rumination or to improve problem solving have potential to reduce the development of depression and could improve psychological and physical health outcomes. Indeed problem solving has been shown to be effective at reducing depression following ACS (Dickens et al., 2013) and has the potential to be used as a therapeutic intervention to offset the adverse effects of ruminating among individuals attending routine cardiac rehabilitation. The clinical and cost-effectiveness of such an intervention would need to be established through high quality randomized controlled trials.

Tables

Table 1: Baseline characteristics of study participants

		Baseline sample n=169*			
		n	%	Median**	IQR
Demographic variables					
Age (years)		169		68.00	16.00
Sex	Male	131	77.51		
Years of education	Secondary *(11 years or less)*	58	38.16		
	Higher *(more than 11 years)*	94	61.84		
Employment status	In employment	65	38.46		
	Not in employment	104	61.54		
Relationship status	In a relationship	122	72.62		
	Not in a relationship	46	27.38		
Lives alone		43	74.40		
IMD	Most deprived *(deciles 1 to 6)*	82	50.31		
	Least deprived *(deciles 7 to 10)*	81	49.69		
History of depression	Yes	16	9.47		
Smoking status	Smoker	18	10.71		

Alcohol use	Never / infrequent *(once a week or less)*	95	57.23		
	Regular *(twice a week or more)*	71	42.77		
Drug use	Never / infrequent *(once a week or less)*	167	98.82		
	Regular *(twice a week or more)*	2	1.18		
Exercise	Never / infrequent *(once a week or less)*	57	34.13		
	Regular *(twice a week or more)*	110	65.87		
Disease variables					
Diagnosis	Unstable angina	47	27.81		
	STEMI	63	37.28		
	NSTEMI	58	34.32		
	Unknown	1	0.59		
Days since index event[***]		161		98.00	67.00
Left ventricular function	Good / normal function	63	47.73		
	Mild dysfunction	42	31.82		
	Moderate dysfunction	21	15.91		
	Severe dysfunction	6	4.55		
NYHA functional classification	No impairment	78	46.99		
	Some impairment *(mild, moderate, severe)*	88	53.01		

Number of diseased vessels (>50% occluded)	0	4	2.37		
	1	70	41.42		
	2	53	31.36		
	3	42	24.85		
Comorbidity score	1 or less	121	71.60		
	2 or more	48	28.40		
Troponin		116		177.50	829.00
CRP	Inflammation low *(<10 mg/L)*	54	59.34		
	Inflammation high *(≥10 mg/L)*	37	40.66		
White cell count	Normal *(<12 x10^{9}/L)*	114	69.94		
	Raised *(≥12 x10^{9}/L)*	49	30.06		
Perseverative negative thinking, depression and quality of life					
RRS brooding		162		7.00	4.00
PSWQ		163		35.00	21.00
PHQ-8		167		2.00	5.00
EQ5D VAS		167		75.00	25.00
EQ5D index value		165		0.81	0.29
SAQ physical limitations		162		80.56	41.72

SAQ angina frequency	167	100.00	20.00
SAQ angina stability	156	100.00	50.00
SAQ treatment satisfaction	164	100.00	15.63
SAQ disease perception	160	75.00	41.67
Possible mediators			
ESSI	169	28.00	6.00
SPSI-R:S positive problem orientation	167	12.00	5.00
SPSI-R:S rational problem solving	167	9.00	5.00
SPSI-R:S negative problem orientation	167	4.00	6.00
SPSI-R:S impulsivity	167	4.00	5.00
SPSI-R:S avoidance	167	4.00	5.00
SPSI-R:S total score	167	13.80	3.40
PES-E	164	2.95	1.09

*N=111 at 6 months. Characteristics of completers vs. non-completers were not significantly different, with the exception that more non-completers at 6 months had raised white cell count (41.1% vs. 24.3%; $\chi2(1)= 4.92$, $p= 0.027$) and raised C-reactive protein (55.6% vs. 30.9%; $\chi2(1)= 5.48$, $p= 0.019$) at hospital admission.

**Median and IQR presented since the majority of continuous variables were non-normally distributed.

***Index event = admission date of most recent hospitalisation for ACS prior to the baseline questionnaires being completed.

Table 2: Staged multivariable regression models: predictors of depression (PHQ-8*) at 6 months

Rumination model (n=106)						Worry model (n=107)					
	β	SE	t	Adj R^2	ΔR^2		β	SE	t	Adj R^2	ΔR^2
Step 1 *F(6,99)=8.93*[a]				0.31		**Step 1** *F(6,100)=8.03*[a]				0.28	
Step 2 *F(7,98)=26.20*[a]				0.63	0.30[a]	**Step 2** *F(7,99)=23.90*[a]				0.60	0.30[a]
Step 3 *F(8,97)=24.68*[a]				0.64	0.02[c]	**Step 3** *F(8,98)=20.83*[a]				0.60	0.00
Age	0.03	0.03	0.53			Age	0.03	0.03	0.38		
Sex	0.09	0.70	1.48			Sex	0.08	0.74	1.28		
IMD	0.01	0.12	0.15			IMD	0.01	0.13	0.09		
Q1 ESSI	-0.23	0.05	-3.22[b]			Q1 ESSI	-0.19	0.06	-2.55[b]		
Q1 NYHA	0.08	0.59	1.22			Q1 NYHA	0.06	0.62	0.94		
History of depression	-0.03	1.06	-0.51			History of depression	-0.01	1.12	-0.15		
Q1 PHQ-8	0.55	0.10	5.90[a]			Q1 PHQ-8	0.66	0.09	7.41[a]		
Q1 RRS brooding	0.20	0.12	2.36[c]			Q1 PSWQ	0.05	0.03	0.63		

*PHQ-8=continuous outcome variable

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

ΔR^2=change in R^2.

Table 3: Summary of mediation analyses for the association of baseline rumination with depression (PHQ-8*) at 6 months

	'Causal steps' regression models**				Bootstrapped estimate of
Proposed mediator	*Path c'*	*Path a*	*Path b*	*Path c*	indirect effect
	Total effect rumination → depression	Rumination → mediator	Mediator → depression	Direct effect rumination → depression	*Path a x b*
ESSI	**1.00[a]**	**-0.41[c]**	**-0.25[a]**	**0.89[a]**	**0.10 (CI=0.00, 0.29)**
SPSI-R:S positive problem orientation	1.00[a]	-0.50[a]	-0.09	-	-
SPSI-R:S rational problem solving	1.00[a]	-0.26	-0.03	-	-
SPSI-R:S negative problem orientation	**1.00[a]**	**0.88[a]**	**-0.46[a]**	**0.60[a]**	**0.40 (CI=0.16, 0.73)**
SPSI-R:S impulsivity	1.00[a]	0.28[b]	0.01	-	-
SPSI-R:S avoidance	1.00[a]	0.27[b]	0.04	-	-
SPSI-R:S total score	1.00[a]	0.44[a]	-0.23	-	-
PES-E	**1.00[a]**	**-0.08[a]**	**-1.13[c]**	**0.91[a]**	**0.09 (CI=0.02, 0.26)**

*PHQ-8=continuous outcome variable

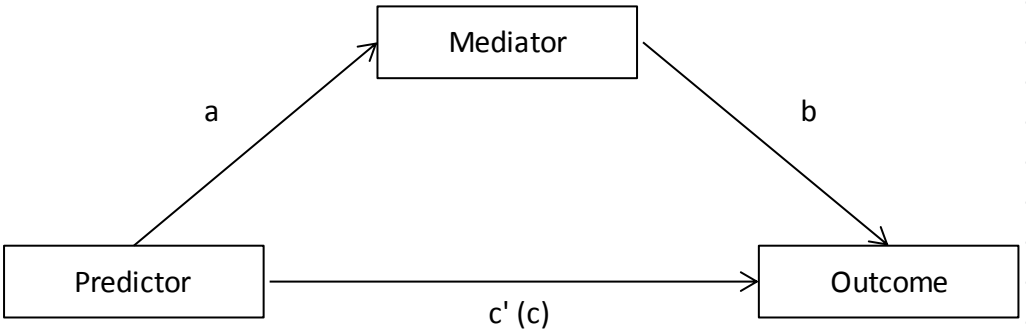
**Unstandardized regression coefficients (B).

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Figures

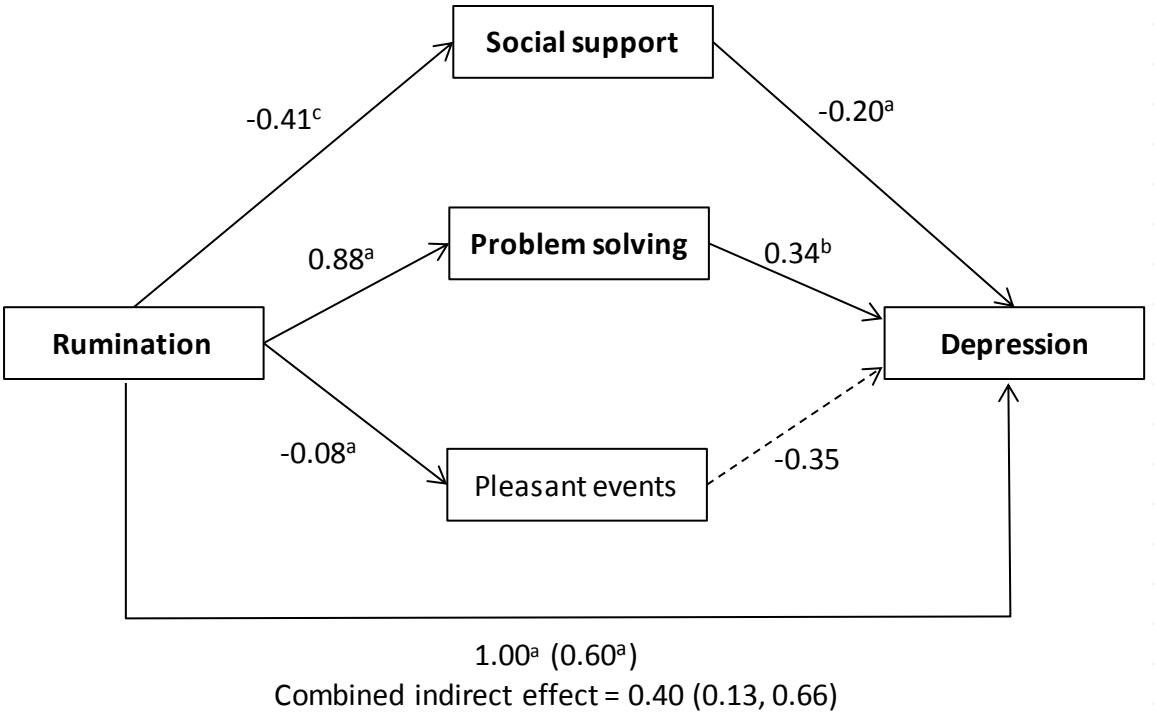
Figure 1

A: Path diagram of mediation



c’ = total effect of predictor on outcome
a = direct effect of predictor on mediator
b = direct effect of mediator on outcome
c = direct effect of predictor on outcome
a x b = indirect effect of predictor on outcome, via mediator

B: Multiple mediation model of the association between baseline rumination and depression (PHQ-8) at 6 months



[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Paths annotated with unstandardised regression coefficients (B).

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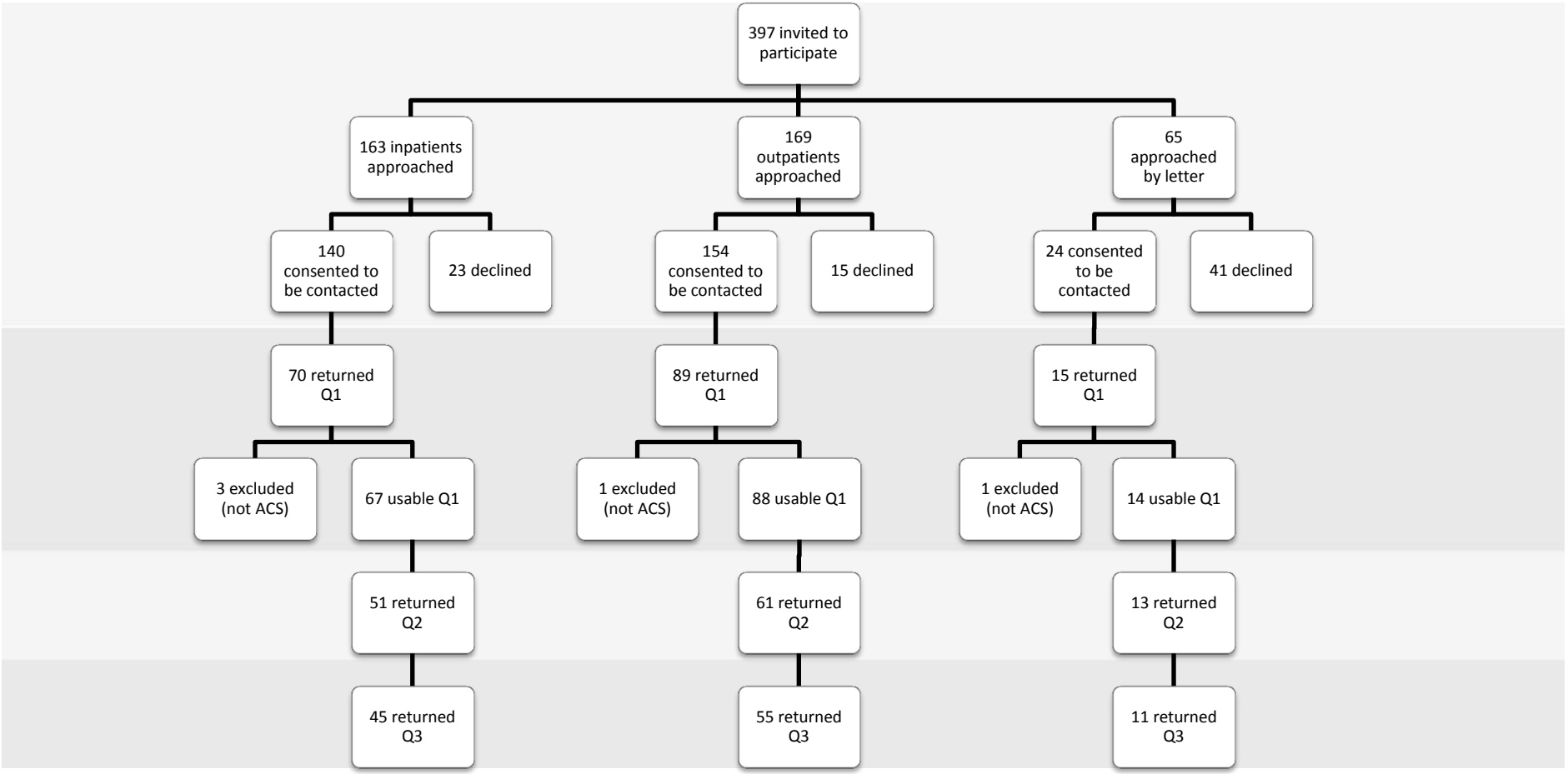
Supplementary Materials

Appendix 1: Flow of participants through recruitment and study completion



Q1=baseline assessments, Q2=2 month assessments, Q3=6 month assessments.

Appendix 2: Staged multivariable regression models: predictors of health-related quality of life (EQ5D index value and EQ5D VAS) at 6 months

Rumination models						Worry models					
Outcome variable: EQ5D index value (n=103)						**Outcome variable: EQ5D index value (n=104)**					
	β	SE	t	Adj R^2	ΔR^2		β	SE	t	Adj R^2	ΔR^2
Step 1 *F(5,97)=10.15*[a]				0.31		**Step 1** *F(5,98)=8.27*[a]				0.26	
Step 2 *F(6,96)=14.61a*				0.44	0.13[a]	**Step 2** *F(6,97)=13.04*[a]				0.41	0.15[a]
Step 3 *F(7,95)=12.45*[a]				0.44	0.01	**Step 3** *F(7,96)=11.65*[a]				0.42	0.01
Age	-0.15	0.00	-1.88			Age	-0.16	0.00	-1.92		
Sex	-0.19	0.04	-2.40[b]			Sex	-0.16	0.04	-2.02[c]		
IMD	-0.12	0.01	-1.57			IMD	-0.13	0.01	-1.65		
Q1 ESSI	0.34	0.00	4.12[a]			Q1 ESSI	0.30	0.00	3.61[a]		
Q1 NYHA	-0.16	0.04	-1.77			Q1 NYHA	-0.12	0.03	-1.39		
Q1 EQ5D	0.41	0.09	4.41[a]			Q1 EQ5D	0.40	0.09	4.42[a]		
Q1 RRS brooding	-0.04	0.01	-0.47			Q1 PSWQ	-0.13	0.00	-1.52		
Outcome variable: EQ5D VAS (n=104)						**Outcome variable: EQ5D VAS (n=105)**					
	β	SE	t	Adj R^2	ΔR^2		β	SE	t	Adj R^2	ΔR^2
Step 1 *F(5,98)=6.91*[a]				0.22		**Step 1** *F(5,99)=6.17*[a]				0.20	
Step 2 *F(6,97)=9.92*[a]				0.34	0.12[a]	**Step 2** *F(6,98)=9.57*[a]				0.33	0.13[a]
Step 3 *F(7,96)=8.88*[a]				0.35	0.01	**Step 3** *F(7,97)=8.83*[a]				0.35	0.02
Age	-0.06	0.18	-0.71			Age	-0.07	0.19	-0.78		
Sex	-0.07	3.84	-0.77			Sex	-0.05	3.82	-0.62		
IMD	-0.11	0.68	-1.37			IMD	-0.11	0.69	-1.36		
Q1 ESSI	0.26	0.29	2.85[b]			Q1 ESSI	0.25	0.27	2.72[b]		
Q1 NYHA	-0.08	3.30	-0.87			Q1 NYHA	-0.06	3.28	-0.69		
Q1 EQ5D	0.37	0.11	3.93[a]			Q1 EQ5D	0.37	0.11	3.93[a]		
Q1 RRS brooding	-0.13	0.54	-1.42			Q1 PSWQ	-0.16	0.12	-1.77		

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Q1=baseline.
ΔR^2=change in R^2.

Appendix 3: Staged multivariable regression models: predictors of cardiac-specific quality of life (SAQ subscales) at 6 months

Rumination models						Worry models					
Outcome variable: SAQ physical limitations (n=100)						**Outcome variable: SAQ physical limitations (n=101)**					
	β	SE	t	Adj R^2	ΔR^2		β	SE	t	Adj R^2	ΔR^2
Step 1 *F(5,94)=11.13*[a]				0.34		**Step 1** *F(5,95)=10.07*[a]				0.31	
Step 2 *F(6,93)=14.55*[a]				0.45	0.11[a]	**Step 2** *F(6,94)=15.08*[a]				0.46	0.14[a]
Step 3 *F(7,92)=12.34*[a]				0.44	0.00	**Step 3** *F(7,93)=13.74*[a]				0.47	0.02
Age	-0.16	0.21	-1.87			Age	-0.21	0.21	-2.53[b]		
Sex	0.06	4.47	0.76			Sex	0.07	4.33	0.93		
IMD	-0.08	0.79	-1.01			IMD	-0.03	0.79	-0.42		
Q1 ESSI	0.18	0.32	2.11[c]			Q1 ESSI	0.13	0.30	1.56		
Q1 NYHA	-0.22	4.21	-2.36[c]			Q1 NYHA	-0.18	4.03	-2.04[c]		
Q1 SAQ	0.41	0.09	4.39[a]			Q1 SAQ	0.45	0.09	5.06[a]		
Q1 RRS brooding	-0.01	0.61	-0.15			Q1 PSWQ	-0.14	0.13	-1.84		
Outcome variable: SAQ angina frequency (n=105)						**Outcome variable: SAQ angina frequency (n=106)**					
	β	SE	t	Adj R^2	ΔR^2		β	SE	t	Adj R^2	ΔR^2
Step 1 *F(5,99)=5.28*[a]				0.17		**Step 1** *F(5,100)=4.95*[a]				0.16	
Step 2 *F(6,98)=10.61*[a]				0.36	0.18[a]	**Step 2** *F(6,99)=9.57*[a]				0.33	0.17[a]
Step 3 *F(7,97)=9.01*[a]				0.35	0.00	**Step 3** *F(7,98)=8.20*[a]				0.32	0.00
Age	-0.05	0.17	-0.55			Age	-0.06	0.18	-0.64		
Sex	-0.09	3.63	-1.09			Sex	-0.08	3.66	-0.89		
IMD	0.01	0.64	0.17			IMD	0.02	0.66	0.20		
Q1 ESSI	0.11	0.26	1.22			Q1 ESSI	0.08	0.26	0.83		
Q1 NYHA	-0.22	3.09	-2.47[c]			Q1 NYHA	-0.21	3.13	-2.37[c]		
Q1 SAQ	0.47	0.10	5.08[a]			Q1 SAQ	0.46	0.10	5.05[a]		
Q1 RRS brooding	-0.02	0.52	-0.21			Q1 PSWQ	-0.05	0.11	-0.58		
Outcome variable: SAQ angina stability (n=94)						**Outcome variable: SAQ angina stability (n=94)**					
	β	SE	t	Adj R^2	ΔR^2		β	SE	t	Adj R^2	ΔR^2
Step 1 *F(5,88)=3.03*[b]				0.10		**Step 1** *F(5,88)=2.24*				0.06	
Step 2 *F(6,87)=2.87*[b]				0.11	0.02	**Step 2** *F(6,87)=2.16*[c]				0.07	0.02
Step 3 *F(7,86)=2.50*[c]				0.10	0.00	**Step 3** *F(7,86)=1.87*				0.06	0.00
Age	0.10	0.33	0.95			Age	0.06	0.35	0.51		
Sex	-0.14	7.63	-1.34			Sex	-0.13	7.76	-1.21		
IMD	-0.03	1.28	-0.33			IMD	-0.04	1.33	-0.34		

Q1 ESSI	0.34	0.50	3.08[b]			Q1 ESSI	0.27	0.49	2.39[c]	
Q1 NYHA	-0.09	5.95	-0.85			Q1 NYHA	-0.09	6.14	-0.81	
Q1 SAQ	0.14	0.12	1.38			Q1 SAQ	0.13	0.12	1.30	
Q1 RRS brooding	0.07	0.96	0.61			Q1 PSWQ	-0.05	0.21	-0.44	
Outcome variable: SAQ treatment satisfaction (n=97)						**Outcome variable: SAQ treatment satisfaction (n=97)**				
	β	SE	t	Adj R^2	ΔR^2		β	SE	t	Adj R^2	ΔR^2
Step 1 *F(5,91)=3.28*[b]				0.11		**Step 1** *F(5,91)=2.89*[c]				0.09	
Step 2 *F(6,90)=4.09*[a]				0.16	0.06[b]	**Step 2** *F(6,90)=3.62*[b]				0.14	0.06[b]
Step 3 *F(7,89)=3.48*[b]				0.15	0.00	**Step 3** *F(7,89)=3.19*[b]				0.14	0.01
Age	0.01	0.17	0.13			Age	-0.03	0.18	-0.25		
Sex	-0.11	3.99	-1.10			Sex	-0.10	4.01	-1.03		
IMD	-0.03	0.66	-0.30			IMD	-0.03	0.68	-0.27		
Q1 ESSI	0.27	0.28	2.57[b]			Q1 ESSI	0.23	0.28	2.11[c]		
Q1 NYHA	-0.10	3.13	-1.01			Q1 NYHA	-0.10	3.19	-0.96		
Q1 SAQ	0.28	0.12	2.66[b]			Q1 SAQ	0.26	0.12	2.54[b]		
Q1 RRS brooding	0.03	0.51	0.33			Q1 PSWQ	-0.08	0.11	-0.83		
Outcome variable: SAQ disease perception (n=96)						**Outcome variable: SAQ disease perception (n=96)**				
	β	SE	t	Adj R^2	ΔR^2		β	SE	t	Adj R^2	ΔR^2
Step 1 *F(5,90)=9.39*[a]				0.31		**Step 1** *F(5,90)=8.37*[a]				0.30	
Step 2 *F(6,89)=12.16*[a]				0.41	0.11[a]	**Step 2** *F(6,89)=11.00*[a]				0.39	0.11[a]
Step 3 *F(7,88)=10.34*[a]				0.41	0.00	**Step 3** *F(7,88)=9.37*[a]				0.38	0.00
Age	0.13	0.19	1.57			Age	0.13	0.20	1.47		
Sex	-0.04	4.43	-0.43			Sex	-0.02	4.51	-0.23		
IMD	0.05	0.74	0.59			IMD	0.04	0.77	0.44		
Q1 ESSI	0.29	0.31	3.17[b]			Q1 ESSI	0.26	0.31	2.78[b]		
Q1 NYHA	-0.13	3.62	-1.54			Q1 NYHA	-0.12	3.72	-1.39		
Q1 SAQ	0.36	0.08	3.86[a]			Q1 SAQ	0.37	0.08	3.99[a]		
Q1 RRS brooding	-0.03	0.60	-0.36			Q1 PSWQ	-0.04	0.13	-0.44		

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Q1=baseline.
ΔR^2=change in R^2.

Appendix 4: Multivariable regression models with time since index event and time since baseline: predictors of depression (PHQ-8) at 6 months

Time since index event (n=102)						Time since baseline (n=106)					
	β	SE	t	Adj R^2	ΔR^2		β	SE	t	Adj R^2	ΔR^2
Step 1 F(7,94)=9.28[a]				0.41		**Step 1 F(7,98)=8.46[a]**				0.38	
Step 2 F(8,93)=21.67[a]				0.65	0.24[a]	**Step 2 F(8,97)=24.87[a]**				0.67	0.30[a]
Step 3 F(9,92)=20.21[a]				0.66	0.01*	**Step 3 F(9,96)=23.67[a]**				0.62	0.02[c]
Age	0.05	0.03	0.72			Age	0.03	0.03	0.47		
Sex	0.13	0.74	1.92			Sex	0.06	0.70	1.02		
IMD	0.03	0.12	0.53			IMD	-0.02	0.12	-0.39		
Q1 ESSI	-0.29	0.06	-3.79[a]			Q1 ESSI	-0.23	0.05	-3.31[a]		
Q1 NYHA	0.08	0.60	1.22			Q1 NYHA	0.06	0.58	0.90		
History of depression	-0.02	1.05	-0.34			History of depression	-0.03	1.04	-0.45		
Time since ACS	0.00	0.00	-0.01			Time since baseline	-0.14	0.01	-2.41[c]		
Q1 PHQ-8	0.52	0.10	5.49[a]			Q1 PHQ-8	0.55	0.09	6.06[a]		
Q1 RRS brooding	0.16	0.12	1.90[p=0.06]			Q1 PSWQ	0.19	0.12	2.30[c]		

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Q1=baseline.

ΔR^2=change in R^2.

Appendix 5: Multivariable regression models with imputed data: predictors of depression (PHQ-8) at 6 months

Rumination model (n=156)				Worry model (n=157)			
	β	SE	t		β	SE	t
Full model *F(8,129.9)=24.42*[a]				**Full model** *F(8,130.7)=21.60*[a]			
Age	0.02	0.03	0.83	Age	0.02	0.03	0.70
Sex	1.11	0.67	1.64	Sex	1.04	0.70	1.49
IMD	0.02	0.12	0.15	IMD	0.01	0.13	0.10
Q1 ESSI	-0.17	0.06	-3.06[b]	Q1 ESSI	-0.14	0.06	-2.46[c]
Q1 NYHA	0.70	0.56	1.24	Q1 NYHA	0.58	0.60	0.98
History of depression	-0.47	1.14	-0.42	History of depression	-0.14	1.16	-0.12
Q1 PHQ-8	0.58	0.10	5.94[a]	Q1 PHQ-8	0.70	0.09	7.40[a]
Q1 RRS brooding	0.28	0.12	2.46[c]	Q1 PSWQ	0.02	0.02	0.64

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Q1=baseline.